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10/564,012	08/11/2006	Tatiana A. Egorova-Zachernyuk	Q92604	3752

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EXAMINER	
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ART UNIT	PAPER NUMBER
1651	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/564,012	EGOROVA-ZACHERNYUK, TATIANA A.	
	Examiner	Art Unit	
	Lora E. Barnhart	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) *1-12 and 17-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/10/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendments

Applicant's amendments filed 3/13/09 to claims 3, 8, and 10 have been entered. No claims have been cancelled or added in this reply. Claims 1-30 remain pending in the current application.

Election/Restrictions

Applicant's election without traverse of Group II, claims 13-16, in the reply filed on 3/13/09 is acknowledged.

It is noted that applicant made no election of species because none of the genera in claims 3, 8, 10, 11, and 26 appear in the elected group. However, if any of these limitations are imported into the claims, applicant should include an election of species as directed in the 1/15/09 restriction in the interest of compact prosecution.

Claims 1-12 and 17-30 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 3/13/09.

Examination on the merits will commence on claims 1-12 and 17-30 ONLY.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 13-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of making proteins from recombinant DNA constructs that are uniformly isotopically labeled on C, H, and O atoms, does not reasonably provide enablement for making isotopically labeled biomolecules of any sort other than proteins or for making non-recombinant isotopically labeled proteins or for making recombinant proteins labeled with isotopes other than ^{13}C, ^{2}H, and/or ^{15}N. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands*, 858 F.2d 731, 737, 8 USPQd 1400, 1404 (Fed. Cir. 1988) (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the level of one of ordinary skill; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. While all of these factors are considered, a sufficient number are discussed below so as to create a *prima facie* case.

The claims are broadly drawn to making a biomolecule in which substantially all atoms are isotopically labeled (see page 7, lines 8-12, of as-filed specification) by culturing mammalian or insect cells such that the biomolecule is produced. The term "biomolecule" must be reasonably interpreted as including any and all molecules that have any effect on any biological system, i.e. any molecule. See M.P.E.P. § 2111.01.

The specification teaches media containing ^{13}C and/or ^{15}N (page 40, lines 7-10, and Example 6 at pages 48-54). The specification in view of the art provides insufficient guidance for using mammalian or insect cells to produce any given biomolecule, e.g. isotopically labeled cyanide, which is toxic to those cells. Even if the scope of the biomolecule is limited to proteins, the specification would fail to be enabling. Numerous proteins include molecules other than carbon and nitrogen, including hemoglobin (a protein that contains iron atoms); the specification makes no allowance for incorporating atoms other than labeled carbon, nitrogen, or hydrogen. It is noted that withdrawn claim 1, from which claim 13 depends, employs a medium in which only the "assimilable atoms" are required to be labeled.

Furthermore, even if the scope of the biomolecule is limited to proteins, the specification cannot fully enable the claims. The specification is limited to methods of producing recombinant proteins from genetically modified insect and mammalian cells; the skilled artisan would have required undue experimentation at the time of the invention to identify conditions conducive to the production of bacterial proteins in mammalian or plant cells, for example. Similarly, applicant does not indicate that the medium of Example 6 affects the expression pattern of any proteins naturally produced by mammalian and/or insect cells.

Applicants present a working embodiment (pages 55-57) in which ^{13}C- and ^{15}N-labeled aquaporin and histamine 1 receptor are produced in Sf9 insect cells by culturing them in a particular medium (described in section 6.1.2 at page 49) and another in which ^{13}C- and ^{15}N-labeled histamine 1 receptor is produced in CHO cells by culturing

them in another medium (described in section 6.2.3 at page 54). While a narrow working embodiment cannot be a sole factor in determining enablement, its limited showing, in light of the unpredictable nature of the art and the lack of direction applicants present, provides additional weight to the lack of enablement in consideration of the *Wands* factors as a whole. Thus, one of ordinary skill in the art would not have a reasonable expectation of success in using the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 13-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 13 depends from withdrawn claim 1, which is improper. Claim 13 should be amended such that it recites the relevant limitations of claim 1.

Claim 13 requires that "substantially all atoms" in the biomolecule produced by the method be "isotopically labeled," but these terms fail to clearly set forth the scope of the degree and nature of labeling required in the end product. At page 7, lines 8-29, of the as-filed specification, these terms are defined functionally ('sufficiently enriched with the desired isotope such that meaningful NMR spectral information can be obtained") or using exemplary conditions ("In general … this means that about 95% or more of the atoms of a given element will be in the desired isotopic form"). The claim and specification do not particularly indicate which degrees and types of labeling are included in the scope of the claims and which are not. Clarification is required.

Claim 13 is drawn to a method for producing a biomolecule, but step (a) does not actually require that any biomolecule be produced. Clarification is required.

Because claims 14-16 depend from indefinite claim 13 and do not clarify the point of confusion, they must also be rejected under 35 U.S.C. 112, second paragraph.

Claim 14 requires that the protein be "soluble," but there is no basis provided for this relative term. Clarification is required.

Claim 15 does not rigorously require that the protein be produced from the expression vector. Clarification is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 13-16 are rejected under 35 U.S.C. 102(b) as being anticipated by Hansen et al. (1992, *Biochemistry* 31: 12713-12718; reference U).

In the interest of compact prosecution, for art rejection purposes only, claim 13 is interpreted as follows:

A method for producing a biomolecule, whereby substantially all atoms in the biomolecule are isotopically labelled, the method comprising the steps of:

(a) growing a culture of mammalian or insect cells capable of producing the biomolecule under conditions conducive to the production of the biomolecule, in a nutrient medium produced by

(i) growing an organism on a mineral medium which supports growth of the organism, whereby in the medium substantially all of the assimilable atoms, for at least one of H, C or N, are isotopically labelled, to produce labelled biomass;

(ii) autolysing the biomass of an organism grown as in (i) to produce an autolysate; and

(iii) composing the nutrient medium by combining the autolysate as obtained in (ii) with further components necessary for growth of the mammalian or insect cells, thereby yielding a nutrient medium; and

(b) recovery of the biomolecule.

This claim language should not be taken as an indication of allowable subject matter or a suggestion og acceptable phrasing. **Applicant is required to amend the claim listing in order to overcome the above indefiniteness rejections.**

Hansen teaches culturing Sp2/0 mammalian hybridoma cells transfected with a urokinase-expressing construct (page 12713, column 2) in a media containing hydrolyzed bacterial and algal extracts that have been labeled with ^{13}C and ^{15}N, then recovering the labeled urokinase (page 12714, column 1). The urokinase produced using Hansen's method allows for study with NMR techniques (page 12715, column 1, and page 12717).

Claim 13 requires growing cells in a nutrient medium that is described wholly using product-by-process limitations. M.P.E.P. § 2113 reads, "Product-by-process

claims are not limited to the manipulations of the recited steps, only the structure implied by the steps."

The structure implied by the process steps should be considered when assessing the patentability of product-by-process claims over the prior art, especially where the product can only be defined by the process steps by which the product is made, or where the manufacturing process steps would be expected to impart distinctive structural characteristics to the final product. See, e.g., *In re Garnero*, 412 F.2d 276, 279, 162 USPQ 221, 223 (CCPA 1979)

The use of 35 U.S.C. §§ 102 and 103 rejections for product-by-process claims has been approved by the courts. "[T]he lack of physical description in a product-by-process claim makes determination of the patentability of the claim more difficult, since in spite of the fact that the claim may recite only process limitations, it is the patentability of the product claimed and not of the recited process steps which must be established. We are therefore of the opinion that when the prior art discloses a product which reasonably appears to be either identical with or only slightly different than a product claimed in a product-by-process claim, a rejection based alternatively on either section 102 or section 103 of the statute is eminently fair and acceptable. As a practical matter, the Patent Office is not equipped to manufacture products by the myriad of processes put before it and then obtain prior art products and make physical comparisons therewith." *In re Brown*, 459 F.2d 531, 535, 173 USPQ 685, 688 (CCPA 1972).

Once a product appearing to be substantially identical is found and an art rejection made, the burden shifts to the applicant to show an unobvious difference. In

this case, the media of Hansen is made by growing bacteria and algae in a labeled medium and promotes production of an isotopically labeled mammalian protein, urokinase, from mammalian cells.

No claims are allowed. No claims are free of the art.

Applicant is requested to specifically point out the support for any amendments made to the disclosure in response to this Office action, including the claims (MPEP 714.02 and 2163.06). In doing so, applicant is requested to refer to pages and line numbers in the as-filed specification, **not** the published application. Due to the procedure outlined in MPEP § 2163.06 for interpreting claims, it is noted that other art may be applicable under 35 U.S.C. § 102 or 35 U.S.C. § 103(a) once the aforementioned issue(s) is/are addressed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lora E. Barnhart whose telephone number is 571-272-1928. The examiner can normally be reached on Monday-Thursday, 9:00am - 5:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lora E Barnhart/
Primary Examiner, Art Unit 1651